generated microarray images..." The specification states that calibration spots are scanned in multiple channels and the scan data analyzed to produce corresponding spot brightness values. See, e.g., page 7, lines 4-6. The brightness values are then manipulated in the manner described in the specification to produce corresponding correction factors, which for the two dye embodiment are the crosstalk ratios Crosstalk A or α_{21} and Crosstalk B or α_{12}. See, e.g., page 7, lines 11 et seq. The crosstalk ratios are then applied to the quantitation data, that is, the brightness values that are obtained from the scan data associated with the remaining spots on the microarray image, by manipulating the quantitation data and the crosstalk ratios in accordance with the equations set forth in the specification on page 7, lines 13-14 for the two dye embodiments, and page 9, lines 2 et seq. for three or more dye embodiments.

Anyone skilled in the art of microarray systems relying on the teachings of the specification can thus readily compute a set of correlation factors based on the brightness values obtained from the calibration dye spot scan data, and apply those factors using the equations set forth in the specification to the quantitation data obtained from analyzing the scan data for the remaining spots on the microarray.

More specifically, the specification provides for a means for measuring an output of each of the output channels, namely, a microarray reader described with reference to Figure 1 and on page 6 with reference to scanning the calibration dye spots. Further, the specification provides for a means for computing a set of correction factors, namely, the sub-system described with reference to Figure 7, which in a known manner analyzes the scan data to produce corresponding brightness values and, in the manner discussed above,

manipulates the brightness values associated with the calibration dye spots to compute the correction factors. The sub-system of Figure 7 also, in the manner discussed above, applies the correction factors to quantitation data, that is, to the brightness values produced by analyzing in a known manner the scan data associated with spots other than the calibration dye spots. The claims are directed to these means as well as their equivalents. Accordingly, the claims satisfy the requirements of section 112.

We now discuss the rejections of claims 1-18 as obvious over the combinations of cited references.

As discussed above, the current system produces the correction factors from scan data associated with calibration dye spots that correspond to the respective dyes. The calibration dye spots, which are produced using the microarray spotting process, are essentially "pure" dye spots, that is, spots that are composed of the maximum labeled-DNA concentration associated with 100% gene expression.

The system scans the respective calibration dye spots on all channels to produce dye images and the image data are then analyzed to produce brightness values that are associated with each of the channels for each of the dyes. The brightness values are then manipulated, as discussed, to produce the correction factors.

As we discuss below, there is no teaching or suggestion in the combinations of references of the use of calibration dye spots, and thus, no teaching or suggestion of the invention as set forth in independent claims 1 and 10 and the claims that depend therefrom.

The Examiner states, in discussing each of the Tulson and Brown references:

> While the reference does not explicitly refer to calibration dye spots using a single pure dye, it is reasonable to infer that single pure dye spots were used for calibration as such dye spots appear to have been routine in the art at the time of the invention. (See at least Schermer et al., US 6,075,613 at Column 2, lines 20-50.)

The cited Schermer reference, which has an inventor in common with the current application, states only that the use of **reference spots with known fluorescence** is known. As discussed in lines 29-30, the scan data associated with the reference spots are used to "quantify the system sensitivity." Thus, the scan data associated with the reference spots are used, for example, to determine a transfer curve for an included attenuator and so forth (See, Schermer et al., Column 1, lines 41 et seq.).

There is no teaching or suggestion in the Schermer reference that the reference spots discussed in the Background section are the single "pure" dye spots, that is, the calibration dye spots, of the current invention. Further, there is no teaching or suggestion that the reference spots are (or even could be) used to produce crosstalk correction factors. Accordingly, there is no teaching in the Schermer reference from which one can infer that calibration dye spots of the current system were used in the Trulson or Brown systems for crosstalk correction.

The Trulson system performs deconvolution operations to handle spectral overlap, and there is no teaching or suggestion of the use of the calibration dye spots in the deconvolution operations. The Brown reference merely states that particular operations

are performed "after correcting for optical crosstalk" (Column 17, line 3), and there is no teaching or suggestion of any method or operation for performing the correction.

The Examiner cites Ginestet in combination with Trulson or Brown and states:

> If pure dye spots for calibration were not used in the nucleic acid microarray methods of Trulson et al. or Brown et al. (as appears to have been common practice as evidenced by Schermer et al.) then it would have been obvious to do so given the teachings of Ginestet which explicitly disclosing such pure dyes for calibration to correct cross-talk due to overlapping dye emission spectra in nucleic acid hybridization.

As discussed above, there is no teaching or suggestion in the Schermer reference of the use of calibration dye spots, and further, there is no such teaching or suggestion in either of Trulson or Brown. As discussed below, the Ginestet reference does not teach or suggest the use of calibration dye spots, and thus, a combination of Ginestet and either of Trulson or Brown does not provide such a teaching or suggestion.

Ginestet describes a system that analyzes M-FISH images. FISH is done on cell or tissue samples, which by definition have indeterminate content. The Ginestet system uses an elaborate filtering and image acquisition process, which involves multiple multiband filter cubes for different subsets of the set of dyes and a relatively complex registration process to align the many images required for processing. (See, Column 3, lines 9 et seq.; Column 5, lines 7 et seq.; Column 8, lines 52 et seq.) As further described in Column 8, lines 2 et seq., and Column 9, lines 27 et seq. the Ginestet system uses the filter cubes to acquire images that use every combination of excitation wavelength and emission wavelength. See also Fig. 6 (inner and outer loops).

To produce a "color spread matrix" for three dyes, the Ginestet system acquires and processes nine images, and to produce the matrix for four dyes the Ginestet system acquires and processes sixteen images, and so forth. See, Column also 11, lines 28 – 31. In stark contrast, the current system uses the calibration dye spots and requires the acquisition and processing of only three images for three dye systems and four images for four dye systems, and so forth.

While the Ginestet reference states that the number of images acquired for calibration can be reduced to the number of dyes "**if** a calibration scene containing easily identifiable single-labeled chromosomes can be obtained" (Column 11, lines 33-34 emphasis added) there is no teaching or suggestion in Ginestet of how to produce such a "calibration scene." As discussed, FISH is done on cell or tissue samples, and it is not readily apparent how a user could obtain a sample, that is, tissue or adjacent cells, that is known to have only predetermined DNA sequences for positive or negative control purposes in the FISH imaging. Indeed, the Ginestet reference states earlier in Column 9, lines 30-31 that "one **cannot** obtain images representative of only a single dye." (emphasis added), and thus, essentially teaches away from the use of such images.

Further, the Ginestet system is not a microarry system, and accordingly, there are no spots produced or scanned by the Ginestet system. There is thus no teaching or suggestion in Ginestet of any type of spot let alone a calibration dye spot.

Assuming the teachings of Ginestet and Trulson or Brown can even be combined, Ginestet does not add to Trulson or Brown the use of calibration dye spots, and thus, the combination does not teach or suggest the invention as set forth in independent claims 1

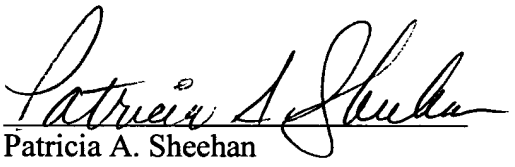
and 10 and the claims that depend therefrom. Accordingly, independent claims 1 and 10 and the claims that depend therefrom should be allowable over the cited combinations.

We do not specifically address the Examiner's rejections of the claims that depend from claims 1 and 10. This should not be construed as acquiescence to the rejections, but as recognition that the rejections are moot based on our remarks regarding the allowability of the independent claims 1 and 10.

In light of the above, we respectfully request that the Examiner reconsider the rejections and issue a Notice of Allowance for all claims.

Please charge any fee occasioned by this paper to our Deposit Account No. 03-1237.

Respectfully submitted,



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